STANFORD UNIVERSITY MEDICAL CENTER
STANFORD, CALIFORNIA 94305 • (415) 321-1200

STANFORD UNIVERSITY SCHOOL OF MEDICINE
*Department of Genetics*
Joshua Lederberg

December 8, 1970

Dr. Ben-Zion Taber
Syntex Research
Palo Alto, Calif.

Dear Ben:

Not long ago, you asked me to comment on procedures that might be set up for the scrutiny of drugs and metabolites for possible mutagenic hazards.

The assay of choice, in most situations, is the "Dominant Lethal Assay"; Some possible limitations are mentioned later in this letter. The rationale of the DLA is that all mutagens, as far as is known, induce dominant lethal mutations as part of a spectrum of effects. These may also include non-lethal chromosome changes and recessive mutations which are much more difficult to assay. The "dominant lethals" are, however, most readily detected, and therefore furnish an economically feasible index of mutagenicity. Dominant lethals are not to be ignored as an aspect of the human damage; however, they operate at the least costly part of the life cycle, and they are examined primarily as an index of the total hazard of a given agent.

The dominant lethal "mutations" themselves include a variety of cell-biological effects -- chromosomal deletions, rearrangements and aneuploidy, as well as point mutations -- which can, if necessary, be analyzed further in the event of a positive response. They share the operational effect of preventing the normal development of the zygote.

The methodology is very well discussed in the enclosed paper by Röhrborn , and by others in the same recent publication, "Chemical Mutagenesis in Mammals", which I recommend to you.

By treating males, then genotype-testing the sperm by mating to control females, one separates the mutagenic effect of the agent from other influences on gestation. One is then often able to use substantial "overloads" of an agent to collect meaningful statistics.

However, there may be special problems in dealing with the sex hormones and their analogues. 1) If they interfere with spermatogenesis to the point of oligospermic sterility, the assay obviously fails
2) One could always argue that an agent that was inactive in males might still perturb meiosis in the egg, the female germ cells being regarded as hormone-specific target tissue, or through secondary consequences of effects on other targets. We would be groping in the dark trying to deal with this issue. However, it may be possible to construct an experimental analogue of the effects reported by Carr, an increase in the incidence of triploidy among abortuses in mothers previously exposed to various agents. I will be happy to discuss these possibilities with you in more detail.

I see limited merit in experimental studies on somatic cell effects, and would recommend these only if no fruitful design came up with germ cells.

Sincerely,